UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,879	01/29/2007	Lynette Robyn Griffiths	FISHR24.001APC	2661

20995 7590 12/09/2010

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
12/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
efiling@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/571,879	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/22/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11,13,14,16-18,20,21,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,11,13,14,16-18,20,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1, 3-9, 11, 13, 14, 16-18, 20, 21, 24, and 25 are pending in the instant application. Claim 21 is withdrawn from consideration as being drawn to a non elected invention. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1, 3-9, 11, 13, 14, 16-18, 20, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method of determining whether a human individual has a predisposition to migraine comprising obtaining a biological sample from said individual that comprises at least one nucleic acid that comprises at least a fragment of exon 8 of the human ESR1 gene that encodes codon 594 and /or at least one nucleic acid that comprises a fragment of

intron 7 of a human progesterone receptor gene and determining whether there is a polymorphism at codon 594 and/or a 306 base pair insertion in intron 7 wherein the presence of the polymorphism indicates that said individual has an increased predisposition to migraine compared to an individual without the polymorphism. The claims are further limited to specific polymorphisms (ESR1 at position 2014 and a 306 base pair insert in PGR). Claim 13 is limited to migraine with aura or migraine without aura. The term "polymorphism" is broadly defined by the specification to include any mutation, insertion or deletion (page 8).

The nature of the invention, therefore, requires the knowledge of predictive associations between migraine and any polymorphism or mutation in codon 594 of the ESR1 gene or any polymorphism which comprises a 306 base pair insertion in intron 7 of the PGR gene any human individual.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and the presence and absence of working examples:

With regard to the specific polymorphisms taught in the specification: The specification teaches 2 different case/control studies which analyzed the association between the ESR1 G2014A SNP (rs2228480) and the PROGINS 306 base pair insertion (rs1042838) in intron 7 of the PGR gene. In the first study of 275 migraineurs and 275 unrelated controls, the specification teaches a statistically significant association between the ESR1 polymorphism and migraine with aura (MA), migraine without aura (MO) in both males in females (page 20). However in the

second replication study of 300 migraineurs and 300 unrelated controls, the statistical significance was only found for MA subgroup in females. For the PGR PROGINS polymorphism, the specification teaches a statistically significant result for MO subgroup in females (page 21) in the first study, but only for the MA subgroup in the second replication study.

With regard to the polymorphisms broadly encompassed by the claims: The specification does not teach how the polymorphisms studied, in either gene, affect the function of either gene or how they are associated with migraine in humans. No common element or attributes of the sequences are disclosed which would permit selection of additional larger insertion polymorphisms in intron 7 of the PGR (as encompassed by the language "polymorphism comprising a 306 base pair insertion) or other polymorphisms at codon 594 of the ESR1 gene as functional polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with migraine is provided. Only a specific nucleotide change has been taught in the specification for each. The specification does not teach how these polymorphisms are associated with migraine for the skilled artisan to be able to predictably identify polymorphisms or mutations that would have the same effect. The polymorphisms shown are therefore not representative of the genus of any polymorphism associated with migraine because it is not clear which polymorphisms or mutations would have the same affect.

The state of the prior art and the predictability or unpredictability of the art:

While the state of the art and level of skill in the art with regard to the detection of any known polymorphic allele is high, the level of unpredictability in associating any particular allele with a specific phenotype is even higher. The high level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

With regard to the specific polymorphisms taught in the specification, it is noted that certain results were not replicated in applicants own follow up study. With regard to the predictability in the art regarding association studies, Lucentini (The Scientist; 2004, vol 24, page 20) teaches that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Similarly, Hegele (Arterioscler. Thromb. Vasc. Biol.; 2002, Vol 22, pages 156-1061) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

In the instant invention, the level of complexity and unpredictability is also borne out in simply establishing that the polymorphisms studied are associated with migraine. As already noted, applicants own replication study failed to provide statistically significant correlations. Further, a number of studies have been undertaken to confirm the findings taught in the specification with little success. With regard to the ESR1 G2014A (rs2228480) polymorphism: Corominas (Corominas et al; European Journal of Neurology, vol 16, 413-415; 2009), Kaunisto (Kaunisto et al; Cephalagia; vol 26, pages 1462-1472, 2006), and Oterino (Oterino et al; Neuroreport, vol 17, pages 61-64, 2006) teach that no association was found for the ESR1 rs2228480 polymorphism. With regard to the PGR PROGINS polymorphism, Corominas teaches that no association was found between this polymorphism and migraine, while Joshi (Joshi et al; Cephalagia, vol 30, pages 311-320; 2010) teaches a protective effect was found. Conclusions drawn by many of these studies are that genetic variants in either gene are not associated with migraine pathogenesis.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of a number of possible polymorphic positions in codon 594 of the ESR1 gene as well as different possible insertions in the PGR gene, including the specific polymorphisms studied to determine whether the alteration are associated with migraine. As neither the prior art nor the specification provide guidance as to which alterations at positions throughout ESR1 or PGR are and are not

associated with migraine, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable, as exemplified by the art cited above. Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims, the extensive negative teachings in the art, and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Response to Arguments

4. The response traverses the rejection. The response asserts that the claims have been amended to encompass detection of two specific polymorphisms and that methods of detecting polymorphisms are described by the specification. However, contrary to the assertions made in the response, the amended claims are broader, and encompass any polymorphism at codon 594 of ESR1 and any insertion comprising 306 based pairs in any region of intron 7 of the PGR gene. Additionally, while the specification teaches how to detect a polymorphism, the specification has not provided a predictable association between the broad genus of possible polymorphisms and risk of developing migraine. The response reiterates the results for the specific ESR1 and PGR polymorphisms studied and asserts that given that the specific alteration at codon 594 of ESR1 taught in the specification leads to such a significant alteration in propensity toward migraine, one skilled in the art would readily recognize that other alterations in codon 594 would similarly lead to an increased propensity toward migraine, and that in combination, these alleles increase the risk of migraine by a factor of 3 and that as such, there is no prima facie showing that the claimed inventions is not enabled. These arguments have been thoroughly reviewed but were

not found persuasive. The arguments made at page 8, regarding the ESR1 polymorphism are merely attorney arguments. The response provides no scientific reasoning as to how the effect of the specific ESR1 polymorphism studied provides any predictability to any polymorphism in codon 594. The specification does not teach how the polymorphisms studied, in either gene, affect the function of either gene or how they are associated with migraine in humans. No common element or attributes of the sequences are disclosed which would permit selection of additional larger insertion polymorphisms in intron 7 of the PGR (as encompassed by the language "polymorphism comprising a 306 base pair insertion) or other polymorphisms at codon 594 of the ESR1 gene as functional polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with migraine is provided. Only a specific nucleotide change has been taught in the specification for each gene. The specification does not teach how these polymorphisms are associated with migraine for the skilled artisan to be able to predictably identify polymorphisms or mutations that would have the same effect. Further, with regard to the specific polymorphisms taught in the specification, it was noted in the previous office action that that certain results were not replicated in applicants ***own follow up study***. The office action further discussed the general unpredictability of the associated technology taught in the prior art, and provided evidence of such unpredictability in a number of follow up studies which did not find any association between the specific polymorphisms taught in the specification and migraine susceptibility. When the claims are analyzed in light of the conflicting studies in the specification (for ESR1, a replication study only found an association in a specific subgroup of females with MA; for Progins, associations were found in conflicting subgroups in the

replication study), the general unpredictability of the associated technology taught in the prior art, as well as the evidence of such unpredictability as taught by the follow-up studies cited, it is clear that undue experimentation would be required of the skilled artisan to make or use the invention as claimed. The rejection is therefore maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner is a hoteling examiner and can normally be reached Mondays, Tuesdays, and Thursdays from 8:00 AM to 2:00 PM, and Fridays from 8:00 AM to 12:00 PM Eastern time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571) 272-0731. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634